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## **Pulmonary Function Test Abnormalities in Pediatric Inflammatory Bowel Disease**

Furlano, Raoul I ; Basek, Pavel ; Müller, Pascal ; Bieli, Christian ; Braegger, Christian P ; Barben, Jürg ; Hammer, Jürg ; Moeller, Alexander ; Trachsel, Daniel

**Abstract:** BACKGROUND Pulmonary involvement in adult patients with inflammatory bowel disease (IBD) seems more common than previously appreciated. Its prevalence and development over time in pediatric IBD patients are largely unknown. OBJECTIVES The aim was to study lung function including fraction of exhaled nitric oxide (FeNO) and transfer capacity for carbon monoxide (TLCO) in pediatric IBD patients and to describe the longitudinal development in a subset of patients with lung function abnormalities. METHODS Sixty-six measurements were made in 48 IBD patients (30 patients with Crohn's disease and 18 with ulcerative colitis) and 108 matched controls. Patients with abnormal TLCO or elevated residual volume/total lung capacity (RV/TLC) ratios were invited for a follow-up. Statistical comparisons were made by nonparametric tests and ANOVA. RESULTS TLCO was decreased in IBD patients [median: 88% predicted (interquartile range, IQR, 22) vs. 99% predicted (IQR 19) in controls]. RV/TLC ratios were mildly elevated in patients with ulcerative colitis [32% (IQR 9) vs. 27% (IQR 8) in controls], and maximum expiratory flows at 50 and 25% of vital capacity were mildly reduced in patients with Crohn's disease. FeNO and disease activity did not correlate with lung function abnormalities. Abnormalities did not consistently persist over a median follow-up period of 34 months. CONCLUSIONS This study supports evidence that variable and fluctuating pulmonary involvement also occurs in pediatric IBD patients. Its clinical significance is unclear. © 2015 S. Karger AG, Basel.

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# Pulmonary Function Test Abnormalities in Pediatric Inflammatory Bowel Disease

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## Key Words

Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Lung function · Fraction of exhaled nitric oxide · Outcome

## Abstract

**Background:** Pulmonary involvement in adult patients with inflammatory bowel disease (IBD) seems more common than previously appreciated. Its prevalence and development over time in pediatric IBD patients are largely unknown. **Objectives:** The aim was to study lung function including fraction of exhaled nitric oxide (FeNO) and transfer capacity for carbon monoxide (TLCO) in pediatric IBD patients and to describe the longitudinal development in a subset of patients with lung function abnormalities. **Methods:** Sixty-six measurements were made in 48 IBD patients (30 patients with Crohn's disease and 18 with ulcerative colitis) and 108 matched controls. Patients with abnormal TLCO or elevated residual volume/total lung capacity (RV/TLC) ratios were invited for a follow-up. Statistical comparisons were made by nonparametric tests and ANOVA. **Results:** TLCO was decreased in IBD patients [median: 88% predicted (interquartile range, IQR, 22) vs. 99% predicted (IQR 19) in controls]. RV/TLC ratios were mildly el-

evated in patients with ulcerative colitis [32% (IQR 9) vs. 27% (IQR 8) in controls], and maximum expiratory flows at 50 and 25% of vital capacity were mildly reduced in patients with Crohn's disease. FeNO and disease activity did not correlate with lung function abnormalities. Abnormalities did not consistently persist over a median follow-up period of 34 months. **Conclusions:** This study supports evidence that variable and fluctuating pulmonary involvement also occurs in pediatric IBD patients. Its clinical significance is unclear.

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## Introduction

Increasing evidence suggests that the prevalence of asymptomatic respiratory involvement is underestimated in adult patients with inflammatory bowel disease (IBD) [1–7], and recent reviews have emphasized that adult pa-

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tients should be systematically monitored for lung disease [3, 8, 9]. In contrast, a recent audit among participants of the EUROKIDS IBD registry, an ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) task force, describing the current state-of-the-art diagnostic work-up in pediatric IBD as well as the underlying 2005 ESPGHAN guidelines, suggest that pulmonary involvement is not considered a feature of pediatric IBD that warrants systematic and regular investigation [10, 11]. In fact, there are insufficient data to determine the prevalence, significance, and evolution of respiratory involvement in the pediatric IBD population. Published studies comprise around 90 children in total, and results are contradictory. Munck et al. [12] reported a persistently reduced transfer capacity for carbon monoxide (TLCO) even during clinical remission in a majority of 25 children with Crohn's disease (CD), and Mansi et al. [13] found bronchial hyperresponsiveness in 10 out of 14 children with CD. In contrast, a recent study from Poland including 25 ulcerative colitis (UC) and 25 CD patients concluded that respiratory involvement is unusual in children with IBD [14].

The primary objective of the current study was to assess the prevalence and clinical significance of pulmonary involvement in children with IBD in a three-center case-controlled study; a secondary aim was to assess the persistence of lung function abnormalities longitudinally.

## Materials and Methods

### Subjects

All children with IBD attending the outpatient gastrointestinal clinics of the participating institutions were eligible for this study. Exclusion criteria were a respiratory tract infection within the precedent 3 weeks, denial or withdrawal of consent, and the inability to perform reproducible lung function measurements. The study was approved by the local ethics committees of the institutional review boards (EK318/06), and parental and patients' written informed consent were obtained from all participants. Each patient was carefully matched to two controls by sex, height, age, and weight. The controls were recruited from patients referred to the pulmonary outpatient clinics for exercise intolerance of unclear etiology or nonspecific dry cough and were not found to have current lung disease. Delayed puberty and growth failure are not uncommon in IBD patients [15]. IBD patients were thus expected to have lower weight and height for age; therefore, recruiting controls matched primarily for height and sex, followed by age and weight, was considered more appropriate to provide optimally matched controls than recruiting age- and sex-matched controls from the general population. This was considered particularly important with regard to TLCO, the primary lung function variable in focus, which is mainly predicted by sex and height in children [16]. All patients and controls were of Caucasian origin.

The first recruited patient was registered in Mai 2004, and patients were recruited up to November 2011. The last follow-up was in June 2013.

### Study Design

All patients underwent clinical assessment, blood sampling for hemoglobin (Hb), and lung function testing including maximum expiratory flow volume curves and body plethysmography, TLCO, and measurement of the fraction of exhaled nitric oxide (FeNO). Patients with an increased residual volume/total lung capacity (RV/TLC) ratio of >30% or with an Hb-corrected TLCO <75% of predicted were invited for a follow-up assessment after a mean interval of  $2.8 \pm 2.8$  years. Clinical IBD activity in CD was documented by means of the abbreviated Paediatric Crohn's Disease Activity Index (PCDAI), which excludes laboratory variables and growth velocity of the original PCDAI but correlates well with the latter [17]. As no pediatric UC activity score was available at the time of study initiation, the Simple Clinical Colitis Activity Index (SCCAI), which had been developed for adult patients, was used for UC patients [18]. In addition, treatment history and respiratory symptoms were documented. Allergic sensitization was derived from the personal history, skin prick testing, and/or specific IgE testing to the most common inhalant allergens (silver birch, timothy, rye, and mugwort pollen, cat and dog dander, *Dermatophagoides pteronyssinus*, and *Cladosporium herbarum*) by immunoallergosorbent testing (ImmunoCAP sx1, Phadia GmbH, Freiburg, Germany).

### Lung Function Testing

FeNO was measured online by the single-breath method using a chemiluminescence NO analyzer (CLD 77 AM, Eco Physics, Dürnten, Switzerland) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines after inhaling NO-depleted ambient air (Denox 88, Eco Physics) [19, 20]. Measurements were made in triplets at 30-second intervals, and the mean was taken for analyses. Spirometry, body plethysmography, and TLCO measurements (MasterScreen and MasterLabPro, Erich Jaeger GmbH, Höchberg, Germany) were performed in accordance with established ATS/ERS guidelines after the completion of FeNO measurements [21–23]. Data were referenced to the normal data by Polgar and Promadhat [24] and Zapletal et al. [25]. TLCO single-breath measurements were corrected for Hb in IBD patients according to the ATS/ERS recommendations [26] and according to the equations proposed by Marrades et al. [27] after conversion to SI units. As blood samples were not obtained from controls, TLCO adjustments were made in the control group for an assumed Hb of 146 g/l in males older than 15 years and for an assumed Hb of 134 g/l for boys younger than 15 years and for girls [28]. Predictions for TLCO and TLCO/alveolar volume (VA) were those referenced by de Jongste et al. [16], and TLCO/VA values were compared to predictive values after Hb correction according to Marrades et al. [27].

### Statistical Analysis

Patient and control characteristics are presented descriptively. Continuous variables are expressed as medians with interquartile ranges (IQR), unless stated otherwise. Normal distribution of the data was checked by visual inspection of Q-Q plots and formally tested by the Shapiro-Wilk test; t tests were used to test mean differences between two groups. Overall differences of group means

**Table 1.** Antropometric and spirometry/body plethysmography data

	All IBD patients (n = 48, 66 mea- surements)	CD patients (n = 30, 38 mea- surements)	UC patients (n = 18, 28 mea- surements)	Controls (n = 108, 122 matched tests)	p value <sup>a</sup>
Age, years	13.6 (12.6; 15.3)	13.4 (12.2; 14.8)	14.5 (12.7; 15.7)	13.5 (12.1; 14.9)	n.s.
Weight, kg	49.5 (40; 55)	48.8 (37; 54)	50.0 (42; 56)	48.0 (38; 55)	n.s.
Height, cm	155 (149; 165)	153 (143; 161)	161 (153; 168)*	156 (149; 165)	n.s.
TLC, l	4.2 (3.4; 5.2)	3.9 (3.2; 5.0)	4.9 (4.0; 5.4)*	4.3 (3.7; 5.2)	<0.05
TLC, %	101.7 (93; 109)	99.6 (90; 107)**	103.8 (98; 109)	103.8 (97; 109)	<0.05
RV/TLC	28.9 (26; 34)	27.8 (23; 33)	31.9 (27; 36)**	26.9 (23; 31)	<0.05
FVC, l	2.9 (2.4; 3.6)	2.8 (2.4; 3.4)	3.2 (2.6; 3.9)	3.1 (2.5; 3.7)	n.s.
FVC, %	93.9 (86; 102)	96.0 (88; 101)	90.9 (82; 105)	97.2 (87; 106)	n.s.
FEV <sub>1</sub> , l/s	2.6 (2.1; 3.2)	2.5 (2.0; 3.0)	2.9 (2.4; 3.5)	2.7 (2.3; 3.2)	n.s.
FEV <sub>1</sub> , %	99.9 (93; 107)	99.9 (92; 104)*	100.4 (95; 109)	107.4 (96; 115)	n.s.
FEV <sub>1</sub> /VC	88.3 (82; 92)	89.4 (84; 93)	87.7 (80; 92)	87.5 (83; 90)	n.s.
MEF50, l/s	3.4 (2.3; 4.3)	3.1 (2.2; 3.9)	4.0 (3.0; 4.9)**	3.4 (2.8; 4.0)	<0.01
MEF50, %	92.7 (80; 103)	89.0 (74; 99)*	101.2 (89; 110)	96.1 (83; 106)	<0.05
MEF25, l/s	1.6 (1.1; 2.2)	1.4 (0.9; 1.8)	2.0 (1.3; 2.3)**	1.6 (1.3; 2.1)	<0.01
MEF25, %	84.3 (65; 106)	75.9 (61; 97)*	98.7 (77; 113)*	90.4 (73; 104)	<0.01

Numbers indicate medians and IQR in parentheses. n.s. = Not significant. <sup>a</sup> p values for overall differences between groups (Kruskal-Wallis test). \* p < 0.05, \*\* p < 0.01; p values for two group comparisons (controls vs. CD and UC, respectively).

were analyzed by one-way analysis of variance (ANOVA) and overall differences of group medians by the nonparametric Kruskal-Wallis test. Being more robust, the latter was selected for data interpretation and reporting of p values. Serial measurements were made in 15 patients, and values were compared by the Mann-Whitney U test. Spearman's rank order correlation was used to explore the relationship between activity scores and lung function measures. All analyses were performed using IBM SPSS Statistics software version 20.0 (IBM Corp., Armonk, N.Y., USA). A p value of <0.05 was considered statistically significant.

## Results

Sixty-six measurements were made in a total of 48 patients aged 13.6 years (IQR 2.7), matched to 108 controls (12 controls being matched to two measurements). Eighteen patients suffered from UC (8 females) with a median SSCAI of 1 [IQR 5.5 (range 0–20)], and 30 had CD (8 females) with a median PCDAI of 5 [IQR 13 (range 0–20)]. Hb was 117.6 g/l [IQR 18.0 (range 71–146)] in the patient group.

There were differences between the groups for TLC% predicted (p < 0.05), RV/TLC ratio (p < 0.05), and maximum expiratory flow values at 50 and 25% (MEF50 and MEF25) of vital capacity (VC; p < 0.01; table 1). Subgroup analyses revealed that increased RV/TLC ratios

were attributable to children with UC (p < 0.01), in whom an increased RV/TLC ratio >0.30 was present in 54% of cases. In contrast, mild reductions of median mid- and end-expiratory flow values were found in children with CD (table 1). However, merely 8% of CD cases had abnormal forced expiratory volume in 1 second (FEV<sub>1</sub>) % predicted values (<80% predicted).

Predicted TLCO values were significantly lower in the IBD group (p < 0.001) and remained significantly lower than in controls after Hb correction according to the 2005 ATS/ERS recommendations [26] (p < 0.01), with 17% of measurements in IBD patients versus 6% in controls being below an arbitrary lower threshold of 75% predicted (table 2). Of note, TLCO values were not significantly lower in CD patients than in controls when applying the correction equations by Marrades et al. [27] (p = 0.24; table 2).

Median FeNO in IBD patients was 11.6 ppb [IQR 7.8 (range 4–78)], with no significant differences between CD and UC (p = 0.9). Allergic sensitization was documented in 13/47 (28%) of IBD patients (UC: 12%, CD: 37%), in 2/8 patients with FeNO 20–30 ppb (4 UC, 4 CD), and in 3/4 patients with FeNO >30 ppb (2 UC, 2 CD). However, neither FeNO nor expiratory flow values were associated with the allergic sensitization in this cohort. Fifty-two of 66 (79%) of FeNO measurements were per-



**Table 2.** Carbon monoxide uptake capacity of the lungs

	All IBD patients	CD patients	UC patients	Controls	p value <sup>a</sup>
TLCO, mmol/min/kPa	6.1 (5.2; 7.7)	5.8 (4.9; 7.7)*	6.3 (5.5; 7.8)	7.1 (6.2; 8.1)	0.06
TLCO, %	80.0 (73; 93)	85.3 (71; 98)**	77.7 (73; 89)***	97.4 (88; 106)	<0.001
Range	37–122	37–122	57–121	58–129	
TLCO Hb-corr, % <sup>b</sup>	88.2 (78; 100)	92.2 (79; 105)*	86.4 (78; 94)***	98.8 (89; 107)	<0.01
Range	39–142	39–118	61–142	63–127	
TLCO Hb-corr, % <sup>c</sup>	94.2 (82; 109)	95.7 (82; 110)	88.9 (77; 99)	97.2 (88; 106)	n.s.
Range	54–145	54–129	58–145	63–127	
TLCO Hb-corr/VA, %	94.0 (90; 99)	93.6 (90; 98)	97.5 (92; 100)	100.1 (97; 102)	n.s.
Range	73–125	76–125	73–117	78–116	

Numbers indicate medians and IQR in parentheses unless otherwise indicated. Hb-corr = Hb correction; n.s. = not significant. <sup>a</sup> p values for overall differences between groups (Kruskal-Wallis test). <sup>b</sup> Hb correction according to MacIntyre et al. [26]. <sup>c</sup> Hb correction according to Marrades et al. [27]. \* p < 0.05, \*\* p < 0.01; p values for two group comparisons (controls vs. CD and UC, respectively).

formed under immunosuppressive or immunomodulatory treatment. There were no significant differences in FeNO between children with or without immunosuppressive or immunomodulatory treatment (p = 0.6).

Various correlation analyses querying interactions of the RV/TLC ratio, FEV<sub>1</sub> % predicted, TLCO, duration of disease, age, FeNO, and clinical activity scores showed a correlation of the RV/TLC ratio with duration of disease (r = -0.5, p < 0.01) and a borderline correlation of the RV/TLC ratio with disease activity in CD (r = -0.3, p = 0.05). No other correlations were found.

Patients with either an abnormal RV/TLC ratio (>30%) or a decreased TLCO value (<75% predicted) at the initial assessment were invited for a follow-up visit, and 18 serial measurements were made with an interval of 2.8 ± 2.8 years. The RV/TLC ratio decreased from 32 ± 6 to 28 ± 5% (p < 0.01). No differences between the two measurements were found for any other variable. Notably, TLCO<sub>% predicted</sub> and expiratory flow abnormalities did not consistently persist over time (fig. 1).

## Discussion

The IBD patients in this cohort showed lower TLCO and mid- and end-expiratory flow values than controls, albeit only a minority of patients had reduced lung function below the normal range. Impaired TLCO was found in both CD and UC patients, while flow reductions were attributable to CD patients, and an increased RV/TLC ratio was seen in UC patients. Longitudinal assessment in

this series did not show persistence of abnormalities over a mean observation period of almost 3 years.

Clinically overt respiratory disease in IBD shows considerable variability, affecting the airways, the parenchyma, and/or the pleura [29–34]. Respiratory symptoms, however, are rare, and bronchopulmonary involvement is assumed to remain clinically silent in the majority of cases. A transbronchial biopsy study in adult UC patients with no concurrent pulmonary symptoms indeed revealed variable degrees of mononuclear cell infiltration and/or fibrosis in 8 out of 10 patients [6]. Bronchoalveolar lavage studies in patients with clinically inactive IBD similarly showed increased counts of inflammatory cells, usually with a mononuclear predominance, implying ongoing pulmonary inflammation even during clinical remission [4–6].

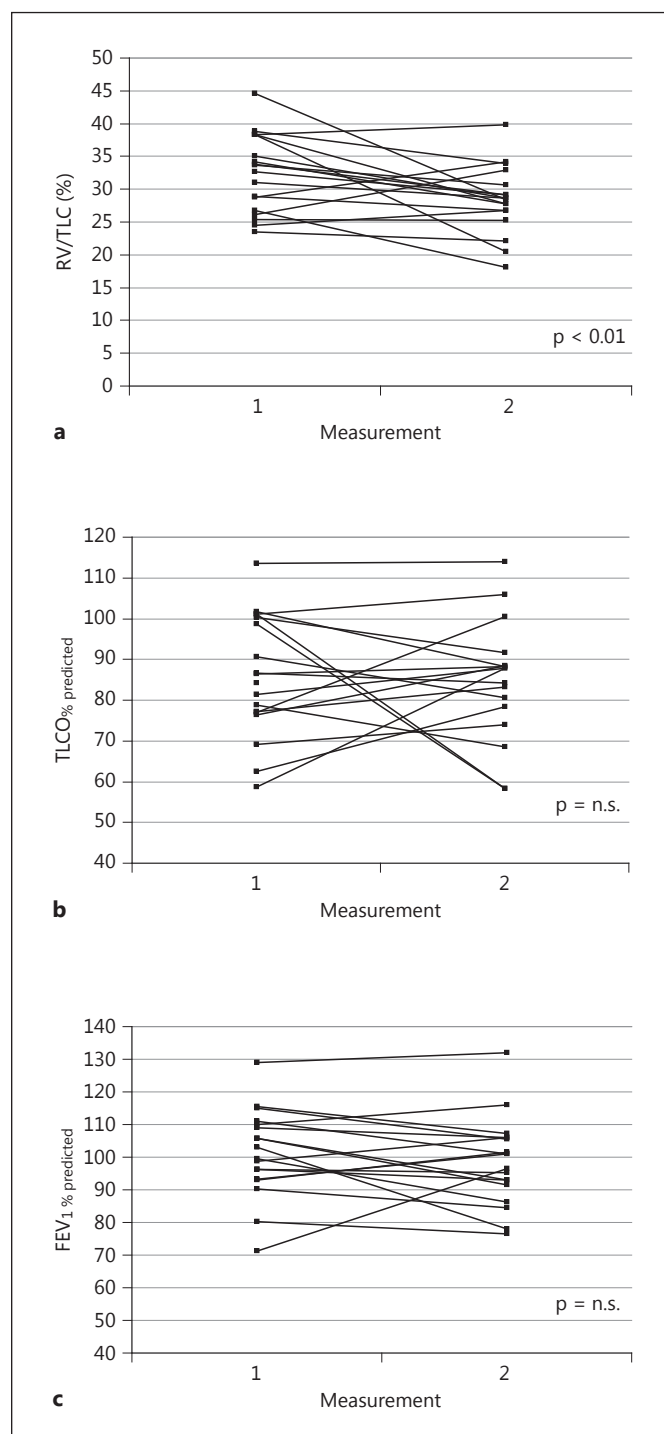
A reduced TLCO is the most frequently reported abnormality in IBD patients. Studies in adults also suggested that lung function changes may correlate with disease activity, but, consistent with the bronchoalveolar lavage studies, persistent lung function abnormalities are also found in a substantial subset of individuals without pulmonary symptoms during IBD remission [1–3, 7, 35–39].

Our results corroborate that TLCO may indeed be mildly reduced in many IBD patients. The biological basis of this TLCO reduction, however, remains unclear. A normal (instead of a reduced) VA/TLC ratio argues against airway obstruction and ventilation inhomogeneity being the underlying pathogenic mechanisms. As both TLCO and the rate constant for CO uptake (TLCO/VA) were reduced in our population, we would preclude that

the impaired TLCO in IBD was due to incomplete VC maneuvers [40]. In theory, the reduced TLCO may be caused by changes in the alveolar membranes or in the pulmonary vasculature such as capillary paucification or intrapulmonary shunting. Current concepts of IBD pathogenesis suggest that an imbalance between defense against and tolerance of the intestinal flora leads to an altered composition and reduced biodiversity of the microbial flora, a deregulated and overshooting immune response, and a disruption of the epithelial barrier function [41–43]. There is evidence suggesting that some immunoreactive cells in IBD do not remain homed in the gut but recirculate to other tissues such as the lung [44], allowing intense cross-talk between intestinal and pulmonary immune cells [45]. Thus, inflammation may contribute to the mildly impaired TLCO.

The present study underscores that TLCO measurement without Hb correction is inappropriate in anemic patients. Blood samples are often reluctantly drawn in children, but Hb correction had a major impact on TLCO results in this cohort, and it is noteworthy that a fair number of published studies did not describe whether and how anemia had been accounted for. As no Hb values were available for the controls in this study, the relatively crude recommended estimations were used subsidiarily [26]. Using the 50th percentile of an alternative Hb reference [46], however, did not change the results of the study.

Airway obstruction both in UC and in CD has been reported in some but not all cohorts [7, 12, 14, 47–50]. We found mildly decreased mid- and end-expiratory flow values in CD patients compared to controls, while the larger airways seemed unaffected as reflected by normal FEV<sub>1</sub> and FEV<sub>1</sub>/VC values. This is in line with a previous study in 30 adult patients which concluded that the function of the small airways was affected in IBD [39], and it concurs with studies reporting air trapping in IBD by imaging studies [3, 33]. However, we could not detect significant air trapping by differentiating functional residual capacity (FRC) measured by plethysmography (FRC<sub>pleth</sub>) from FRC measured by Helium dilution (FRC<sub>He</sub>) [22], neither were RV/TLC ratios correlated with disease activity, which could imply incomplete exhalation due to abdominal discomfort. Only three studies in adults so far have reported RV/TLC ratios, two of which described elevated RV/TLC ratios [3, 48, 51]. The inherently large variability in measured peripheral airway flows needs to be taken into account when interpreting MEF50 and MEF25, rendering these results less robust. Ventilation inhomogeneity measures might be a valuable



**Fig. 1.** Serial measurements of the RV/TLC ratio, TLCO% predicted, and FEV<sub>1</sub> % predicted (median interval between measurements: 2.8 years; n = 18). n.s. = Not significant.

tool to corroborate subclinical disease activity at the level of the small airways [52].

A few studies have revealed an increased prevalence of bronchial hyperreactivity in both atopic and non-atopic IBD patients [1, 13, 53]. We did not test for bronchodilator responsiveness, as the protocol foresaw administration of salbutamol only when baseline spirometry was suggestive of airway obstruction. We therefore cannot exclude that asthma or atopy contributed to airway obstruction in some of our CD patients, but neither the presence of atopy nor FeNO were significantly related to lung function results. An increased prevalence of atopy in IBD patients has been described in some but not all previous studies [1, 53, 54]. The apparent contrariness of an increased atopy prevalence in CD and its alleged TH<sub>1</sub>-dominated immunology has recently been put into new perspective with the recognition of the complexity of immunologic reactions involved in IBD [43].

The misdirected inflammatory activity that characterizes IBD is associated with an overproduction of reactive oxygen and nitrogen metabolites in the gut [55–57]. These reactive species contribute to mucosal injury, reduced perfusion, poor wound healing, and maintenance of chronic inflammation [55]. In the lung, FeNO correlates reasonably well with eosinophilic airway inflammation, which has facilitated monitoring of disease activity in atopic asthma [58, 59], but FeNO is of limited value for assessing mucosal airway inflammation in noneosinophilic airway disease [60].

It has been hypothesized that nitrogen pathways may contribute to IBD-associated lung disease, and its metabolites may serve as markers of pulmonary involvement in IBD [47, 50]. Since Koek et al. [47] have reported a significant correlation of FeNO with disease activity in 55 adult IBD patients, a number of subsequent studies evaluating FeNO as an indicator of pulmonary involvement in IBD have revealed conflicting results [14, 48, 50]. UC

seemed to be associated with higher FeNO levels than CD [14, 47, 48]. The mean FeNO levels associated with IBD in positive studies, however, were low, in the range of 10–30 ppb, and most patients were under some immunomodulatory treatment. As FeNO is sensitive to corticosteroid treatment in most allergic asthma patients [61], it may be speculated that immunosuppressive IBD therapy affects FeNO levels. Alternatively, however, the negative FeNO results in this study may imply that airway inflammation in IBD, if present, is not predominantly an eosinophilic inflammation [53, 60].

Strengths of this study are the size of the cohort, which substantiates the data on pulmonary involvement in pediatric IBD patients and allows a comparison of UC with CD, and the inclusion of longitudinal data. Weaknesses are that we were not able to assess bronchial hyperresponsiveness and that follow-up data were available for a limited number of patients only.

In conclusion, the present study supports existing evidence that pulmonary function abnormalities in IBD do occur in children and adolescents, irrespectively of intestinal disease activity. Lung function changes, however, are usually very mild and do not seem to persist longitudinally. These abnormalities suggest variable and fluctuating pulmonary involvement in pediatric IBD and may thus add to our understanding of IBD, but clinical impact during childhood seems limited. We thus argue that at the time being, regular lung function testing in pediatric IBD patients without respiratory symptoms is not mandatory in clinical routine.

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